POLICY AND COMMUNICATIONS BULLETIN
THE CLINICAL CENTER

Medical Administrative Series

M97-1 14 February 1997

MANUAL TRANSMITTAL SHEET

SUBJECT: Protocol Cost and Performance

1. Explanation of Material Transmitted: This issuance transmits the revised policy of the Clinical Center regarding the review of protocols for cost and effectiveness. The revision was approved by the Medical Board at its meeting on 5 November 1996.

2. Material Superseded: MAS M94-12, dated 30 December 1994

3. Filing Instructions: "Other" Section

   Remove: No. M94-12, dated 30 December 1994

   Insert: No. M97-1, dated 14 February 1997

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BACKGROUND

As an institution in the forefront of biomedical research in the United States, the National Institutes of Health (NIH) is obligated to ensure that the scientific investigations carried out on its campus are of the highest quality. As a government facility, the NIH must also exercise its fiduciary responsibility by ensuring that the Federal funds expended for that research are used appropriately and carefully.

With regard to the clinical research carried out on the NIH campus, it is the stated policy of the Medical Executive Committee that no person shall receive care at the Clinical Center unless he or she is enrolled in an active, approved protocol. Protocols thus control access to the care provided and the funds expended for that care. It is essential, therefore, that a system be in place to review the clinical studies carried out at the Clinical Center, to ensure that they are being conducted in conformance with their original purpose and plan, and to monitor their cost-effectiveness.

While every effort should be made to preserve the independence of the research carried out by the biomedical scientists in the Institutes, Centers, and Divisions (ICDs) of NIH, an institution-wide system is necessary to make sure that the necessary reviews are carried out.

POLICY

Prospective and retrospective reviews will be conducted twice a year by the Director and staff of the Clinical Center with each ICD Scientific Director and Clinical Director for all active Clinical Center protocols. The purpose of these reviews will be to monitor protocol costs and performance. These reviews supplement the continuing (annual) reviews of protocols conducted by the Institutional Review Boards.

CONSIDERATIONS

General

1. Since only patients who are enrolled in an active, approved protocol will be admitted to the Clinical Center, it will be necessary for active protocol numbers to accompany requests for admission and all orders for tests and procedures.

2. There are three types of intramural clinical protocols:

   a. Research protocols include Phase I through Phase IV clinical trials, as well as protocols designed to study normal human biology and disease pathogenesis. Such protocols may have multiple components including provisions for screening, drug trials, physiological investigations, natural history, and long-term effects of drugs.

   b. Screening protocols are designed to determine if individuals may be suitable candidates for inclusion in one or another study being carried out by an Institute. The NIH does not support a rigid quota of patients to be admitted for screening purposes, since this may vary widely among ICDs and within an ICD over time. Furthermore, specific screening protocols may be written for long-term accrual of cohorts of patients with interesting, unexplained disease presentation for the purpose of identifying new syndromes. However, the projected number of patients to be accrued to such screening protocols must be estimated in advance and subsequently monitored.

c. Training protocols provide the opportunity for staff physicians and other health workers to follow particular types of patients in order to maintain or increase their professional skills. The projected number of subjects to be accrued to such training protocols must be indicated in advance and subsequently monitored.

All protocols will be written, and will indicate what patients are being admitted for. So-called "omnibus" protocols will be phased out of the NIH portfolio of intramural clinical protocols at the time of their annual review. The Clinical Center will provide ICD Scientific Directors and Clinical Directors with a prospective estimate of the costs of all new protocols and a retrospective statement of costs and patient accrual of all ongoing protocols. To obtain this prospective cost estimate, ICDs will submit protocols to the Clinical Center Budget Office concurrently with the submission to the IRBs.

3. All protocols will be reviewed annually and updated to reflect new areas of research being developed. At the time of the annual review, protocols will be revised to assure that any tests being performed that are not already defined in the original protocol are defined in the document.

4. Each protocol will be required to define thoroughly the care and procedures required for the study. Clinical research must take place within the context of overall excellence in patient care. For this reason, it will be necessary in some cases to provide appropriate clinical care not specified by the protocol (some of which may be unanticipated) to avoid fragmentation of care and to ensure optimal patient management. While the provision of care which is not specifically protocol-directed is at the discretion of the patient care team, the Senior Attending physician should consult with the Institute Clinical Director when either the propriety or expense of such care might warrant consultation.

5. The NIH intramural research program includes fourteen Institutional Review Boards (IRBs) whose primary mandate is to protect the rights and welfare of human subjects enrolled in research protocols. Protocol review is designed to assure that risks to subjects are minimized by using procedures that are

consistent with sound research design; that risks to subjects are reasonable in relation to anticipated benefits; that selection of subjects is equitable; that appropriate informed consent is obtained from each prospective subject; and that, when appropriate, Data Safety Monitoring Boards are established to safeguard the safety of study participants and the scientific integrity of clinical trials.

The IRBs function in accordance with the terms and conditions of the NIH Multiple Project Assurance (MPA), the NIH policy document that describes the intramural program's compliance with the regulations of the Department of Health and Human Services for the protection of human subjects (45 CFR 46). The NIH Office of Human Subjects Research provides oversight of the activities of the IRBs to ensure their compliance with the MPA.

IRBs conduct initial and annual review and approval of all research protocols to be carried out in the Clinical Center. Proposed changes in protocol implementation must receive IRB review and approval before they can be put into effect.

In determining whether an IRB-approved protocol should be implemented, Protocol Implementation Review Committees (PIRCs) are charged with the responsibility for ensuring that:

a. IRB minutes fully reflect the IRB's deliberations and document review and approval of a protocol in accordance with 45 CFR 46.

b. Where appropriate, additional safeguards have been provided for human subjects, as set forth in subparts A, B, C, and D of 45 CFR 46.

c. The protocol is consistent with ICD research objectives and is likely to yield knowledge of importance to the mission of the NIH.

d. All collaborative, cooperative, or multi-site arrangements, including Cooperative Research and Development Agreements (CRADAs) are fully documented and free of conflict of interest.

6. The reviews carried out by the Institutional Review Boards (IRBs) and Protocol Implementation Review Committees (PIRCs) will include review of accrual of women and minority subjects and may include an examination of performance. IRB reviews are carried out to protect the rights and welfare of human subjects, assisted by Data Safety Monitoring Boards when appropriate. PIRCs ensure that proper procedures have been followed in a protocol's review and that the proposed research is consistent with the mission of the NIH. All new protocols receive review and approval by an ICD PIRC after IRB review and approval but before implementation.

PROCESS

1. Twice a year, the Director and staff of the Clinical Center will meet with each ICD Scientific Director and Clinical Director to review all ICD protocols. During these reviews, information will be provided by the Clinical Center to enable the ICD to conduct retrospective and prospective reviews of protocol costs and performance.

   Retrospective Review

   Information to be supplied to the ICD for the retrospective review of protocols will be provided in tabular form (Attachment 1) and will include the protocol number, approval date, title, type (i.e., research, screening, or training), principal investigator and branch, projected study cost, proposed number of study subjects, costs to date, subjects accrued to date, costs in the past year, the sex and ethnic makeup of the subjects accrued to date, and the number of subjects who are NIH employees or members of their immediate family. These data will provide the ICD with the information necessary for an effective review of the protocol, thus enabling the Scientific Director and Clinical Director to determine whether or not the study is proceeding as planned, what the study is costing the ICD, and whether the study conforms with NIH objectives of diversity in patient accrual.

   Prospective Review

   The Clinical Center will provide a summary table (Attachment

2) with information on all new protocols under review or recently initiated. This table will list, for each study: the title, protocol number (if assigned), principal investigator, target number of subjects, the number targeted for the first year, the projected duration of the study, the Clinical Center department(s) that will be highly affected by the study, and the projected cost. This information will allow an ICD to determine if it can afford to start or to continue a particular protocol.

2. If a protocol involves two or more Institutes, the Clinical Center will provide data on cost and patient accrual to all Institutes.

3. Each ICD will devise a process for annual review of its protocols, based on the data supplied by the Clinical Center as described above. This review will enable the ICD to evaluate costs and to make adjustments in its accrual rates to comply with the study's goals. The ICD review process will assure that the Clinical Directors and Scientific Directors provide ICD Directors with an assessment of the annual review. Each ICD's review process will be evaluated for review quality by the Director, Clinical Center (who is also the NIH Associate Director for Clinical Research) and the NIH Deputy Director for Intramural Research.

4. Annually, ICDs will complete an Intramural Management Controls Evaluation Survey, designed to help them comply with all regulations and policies related to clinical research. A form designed to assist in this survey is shown as Attachment 3.